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COMPLETE SPECIFICATION

(54) SUBSTITUTED IMINO-DIACIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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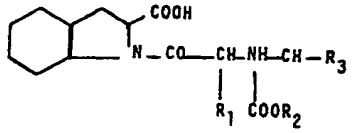
Price 90p

The present invention relates to new substituted iminodiacids, and in particular to substituted perhydroindoledicarboxylic acids, their preparation and pharmaceutical compounds containing them.

The invention relates specifically to the compounds with the general formula:



wherein:

R_1 represents a lower alkyl group having from 1 to 4 carbon atoms,

R_2 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms,

R_3 represents a straight or branched alkyl group, a mono- or dicyclo-alkyl group, each of these groups having a maximum of 9 carbon atoms in total, or a substituted alkyl group of the formula:

$$-(CH_2)_p-S-\underset{\displaystyle R_4}{\underset{|}{CH}}-R_5$$

in which:

R_4 = H, a lower alkyl (C_1 to C_4) or a cycloalkyl (C_3 to C_6)

R_5 = H, a lower alkyl (C_1 to C_4), a cycloalkyl (C_3 to C_6) or an alkoxycarbonyl and

p = 1 or 2

The compounds of the invention contain at least one carboxy group: two in the case where R_2 = H; and at least one salt-forming amino group. The invention thus also relates to the salts of the compounds of the formula (I), especially those obtained with a therapeutically compatible inorganic or organic base.

The invention also relates to the addition salts of the compounds of formula (I), especially those obtained with a therapeutically compatible inorganic or organic acid.

The compounds of formula (I) contain at least 3 asymmetric carbon atoms. Depending on the position of the substituents and the degree of hydrogenation, there are from 3 to 6 centres of asymmetry. The racemic

compounds may be divided into their diastereoisomeric or epimeric mixtures, or resolved into their enantiomers in a known manner. The various isomers form part of the invention, as do the racemic compounds.

The compounds preferred are those corresponding to formula (I) in which R_3 is a straight or branched (C_3 to C_8)-alkyl group, a (C_4 to C_8)-cycloalkylalkyl group, or a substituted alkyl group $-CH_2-S-CHR_4R_5$ with R_4 = H or an alkyl group and R_5 = an alkoxycarbonyl group, the alkyl and alkoxy groups having from 1 to 4 carbon atoms. In addition, R_1 may usefully be a methyl radical.

The compounds according to the invention, and also the salts thereof, have interesting pharmacological properties. In particular, they have an inhibiting effect on certain enzymes, such as the carboxypolypeptidases, the encephalinases or kininase II. They inhibit particularly the transformation of the decapeptide angiotensin I to the octapeptide angiotensin II, which is responsible for certain cases of arterial hypertension, by acting upon the converting enzyme.

The therapeutic use of these compounds thus makes it possible to reduce or even eliminate the activity of these enzymes responsible for hypertension or cardiac

insufficiency. The effect on kininase II results in an increase in the circulating bradykinin and also a reduction in the arterial pressure by this means.

The invention also relates to the pharmaceutical compositions which contain as active ingredient at least one compound of the general formula I or one of its physiologically tolerable addition salts with an inorganic or organic base or acid, in conjunction with an inert, non-toxic, pharmaceutically acceptable carrier.

For therapeutic use, the compounds of the general formula I or the salts thereof are prepared in the form of pharmaceutical preparations suitable for intravenous or oral administration. In addition to the active ingredient, the pharmaceutical compositions according to invention contain one or more inert, non-toxic carriers suitable for pharmaceutical use, and/or a binding agent, an aromatising agent, a disintegrating agent, a sweetener, a lubricant or a liquid excipient suitable for intravenous administration.

The pharmaceutical compositions according to the invention may also contain another active ingredient having a synergistic or complementary effect.

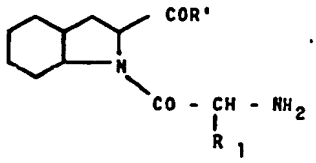
Among the latter active ingredients which may be

mentioned are a diuretic and, in particular, a saliuretic, such as for example a thiazide, a dihydrothiazide, a chlorosulphamide, a dihydrobenzofuran 2-carboxylic acid or a derivative of phenoxyacetic acid. Examples of such compounds are N-(3'-chloro-4'-sulphamoylbenzamido)-2-methylindoline, ethacrynic acid and furosemide.

It is also possible to add α-adrenolytic substances such as prazosin or any other anti-hypertensive substance.

The useful posology may vary widely, depending on the age and weight of the patient, the severity of the symptoms and the method of administration. Oral administration is preferred, but intravenous administration is also perfectly suitable for the treatment of hypertension. In general terms, the unit dose will preferably range between 5 and 100 mg.

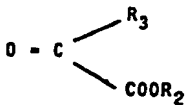
The invention includes a process for the preparation of the compounds of general formula I, which process comprises subjecting an alkyl ester of perhydroindole dicarboxylic acid of the general formula II:



(II)

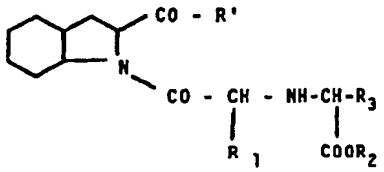
wherein the meaning of the symbol R_1 remains the same as in formula I,

and R' represents a lower alkoxy or hydroxy radical, to a reductive alkylation reaction by means of a compound of the general formula III:



(III)

wherein the meaning of the substituents R_2 and R_3 remains the same as in formula I, in order to obtain an amine of the general formula IV:



(IV)

wherein R' has the meaning given previously for formula II and the symbols R_1, R_2, R_3 retain the meanings provided before,

and after reductive alkylation the intermediate compound obtained is subjected, if necessary, to the usual deprotection processes, such as for example total or partial saponification and/or hydrogenolysis, and is thus converted into a compound formula (I).

The compounds of the general formula II are described in or may be synthesised in accordance with the European Patent Application published under No. 0031741. The above-mentioned reductive alkylation uses the process described by R.F. BORCH, M.D. BERNSTEIN, and H. DUPONT DURST, JACS 93, 2897 (1971). The process is preferably carried out in an alcoholic medium and in the presence of a neutral dehydrating agent and of an organic or inorganic cyanoborohydride.

The following example illustrates the preparation process, but does not result in obtaining a compound of the invention.

(3S)-2-[N-(1-carboxyethyl)-(S)-alanyl]-3-carboxy-1, 2, 3, 4-tetrahydroisoquinoline.

Step A

Laevorotatory tetrahydroisoquinoline-3-carboxylic acid.

15 g of (S)-β-phenylalanine are introduced into a three-necked flask surmounted by a condenser and then 34 ml of a 40% solution of formaldehyde, and 105 ml of concentrated hydrochloric acid are added.

The vessel is heated for 30 minutes over a boiling water-bath. A clear solution is thus obtained, the reaction medium is allowed to cool to room temperature, and then 15 ml of formaldehyde and 30 ml of concentrated hydrochloric acid are added thereto. The mixture is then heated for 3 hours under reflux, and afterwards allowed to cool. The precipitate is then separated off by filtration. After drying without heat, it is taken up in 200 ml of boiling water and 400 ml of hot ethanol. The solutions are combined and neutralised by adding a 10% ammonia solution.

Tetrahydroisoquinoline-3-carboxylic acid crystallises. The crystalline mixture is left to stand overnight in a refrigerator, and then the precipitate is separated off, centrifuged and washed with ethanol. 17.3 g of crude product are thus obtained. The product is dried under vacuum over phosphoric acid.

Analysis $C_{10}H_{11}NO_2$ = 177

	C%	H%	N%
Calculated	67.78	6.26	7.90
Found	66.87	6.20	7.96

Infra-red spectrum

NH_2^+ Band at 2800 - 2400 cm^{-1}

COO^- Carbonyl band at 1630 cm^{-1}

Rotatory power

$\alpha_D = -108^0$ (c = 2.2 normal NaOH)

Step B

(3S)-methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride.

In succession 5 g of tetrahydroisoquinoline 3-carboxylic acid and 30 ml of methanol are introduced into a three-necked flask. 6 g of thionyl chloride are added to this suspension by pouring carefully, taking care that the temperature does not exceed 0, + 5^0. The addition takes approximately 10 minutes. After the addition is com-

pleted, stirring is continued for 2 hours at room temperature, and then the mixture is heated to reflux for 1½ hours. Once the mixture has dissolved completely, heating is discontinued and the mixture is then evaporated to dryness. The residue is taken up three times in methanol and then evaporated to dryness. Finally, 8 g of colourless crystals are obtained and purified by trituration with ether. The crystals are separated off by filtration, centrifuged, washed with ether and dried. 6.4 g of methyl tetrahydroisoquinoline-3-carboxylate hydrochloride are thus obtained.

Analysis $C_{10}H_{13}NO_2ClH$ = 227.69

	C	H	N	Cl%
Calculated	58.03	6.20	6.15	15.57
Found	57.79	6.46	6.38	15.67

Infra-red spectrum

Carbonyl band at 1735 cm^{-1}

NH_2^+ band at 2800 - 2400 cm^{-1}

Step C

(3S)-2-[(S)-tert.butoxycarbonylalanyl]-3-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline.

6.01 g (0.0264 mol) of the hydrochloride prepared in the previous step are dissolved in 50 ml of water and the solution is rendered alkaline to pH 11 with NH_4OH, and then extracted with 2 x 50 ml of sulphuric ether. The combined ether solutions are dried over calcium sulphate, filtered and evaporated to dryness. The residual amino ester (5.04 g) is dissolved in 30 ml of dimethylformamide and this solution is added to a stirred solution of 5 g (0.0264 mol) of (S)-tert.-butoxycarbonylalanine in 30 ml of dimethylformamide cooled to 0, + 5°C. In succession 3.6 g (0.0264 mol) of 1-hydroxybenztriazole dissolved in 40 ml of dimethylformamide, and then 5.45 g (0.0264 mol) of dicyclohexylcarbodiimide dissolved in 30 ml of chloroform are added to the solution obtained.

The reaction mixture is stirred for 18 hours whilst being allowed to return to room temperature. The dicyclohexylurea which is formed is filtered and the filtrate, evaporated to dryness under 0.1 mm Hg, leaves a residue which is redissolved in 50 ml of ethyl acetate and filtered again to separate off a second run of dicyclohexylurea. The filtrate is washed successively with 80 ml of a saturated aqueous solution of NaCl, 2 x 40 ml of a 10% aqueous solution of citric acid, again with 80 ml of a saturated aqueous solution of NaCl, 2 x 40 ml of a saturated aqueous solution of $NaHCO_3$, and finally with a saturated aqueous solution of

NaCl until neutral.

The organic phase is dried over $CaSO_4$, filtered and evaporated to dryness under vacuum. The evaporation residue is the desired product:

Weight : 9.1 g (95%)

Melting point : 98-100° (Kofler)

Analysis $C_{19}H_{26}N_2O_5$

	C	H	N%
Calculated	62.97	7.23	7.73
Found	63.15	7.05	7.97

Step D

(3S)-2-[(S)-tert.butoxycarbonylalanyl]-3-carboxy-1,2,3,4-tetrahydroisoquinoline.

1.45 g of (0.004 mol) of the compound prepared in the previous step are dissolved in 20 ml of methanol, and 4.4 ml (0.004 mol) of normal aqueous sodium hydroxide solution are added to the resulting solution.

The solution is left for 20 hours at room temperature. The methanol is evaporated under vacuum by water jet pump and the residue is taken up in 20 ml of water.

After extraction of the unsaponified material by means of ethyl acetate, the aqueous phase is acidified with 4.4 ml of normal HCl. The precipitate which forms is extracted with 2 x 20 ml of ethyl acetate which is dried over $CaSO_4$, filtered and evaporated. The residue obtained is the desired product:

Weight : 1.3 g (93%)

Analysis $C_{18}H_{24}N_2O_5$

	C	H	N%
Calculated	62.05	6.94	8.04
Found	61.54	6.93	7.78

Step E

(3S)-2-[(S)-alanyl] -3-carboxy-1,2,3,4-tetrahydroisoquinoline.

1.1 g (0.00316 mol) of the derivative prepared in the previous step are stirred at + 5°C with 4.5 ml of trifluoroacetic acid whilst protected from humidity.

The resulting solution is concentrated to dryness under 0.1 mm Hg. The crystalline, hygroscopic evaporation residue is the desired product, in the form of the trifluoroacetate solvated by means of 0.5 mol of tri-

fluoroacetic acid:

Weight : 1.3 g (98%)

Analysis $C_{32}H_{35}F_9N_4O_{12}$

	C%	H%	N%
Calculated	45.83	4.21	6.68
Found	45.99	4.62	6.55

0.7 g (0.0019 mol) of the above trifluoroacetate are transformed into 0.45 g (94%) of the corresponding free amino acid by being passed over 50 g of sulphonated resin (Dowex 50 W x 8 H^+), followed by washing out with 500 ml of normal ammonia solution.

Melting point : 170°C (decomposition).

Step F

(3S)-2-[(S)-N-(1-carboxyethyl)-alanyl]-3-carboxy-1,2,3,4-tetrahydroisoquinoline.

0.849 g (0.0034 mol) of 2-[(S)-alanyl]-3-carboxy-1,2,3,4-tetrahydroisoquinoline are dissolved in the presence of 1.9 g (0.0216 mol) of pyruvic acid at 25°C in 22 ml of normal sodium hydroxide solution and 50ml of pH 7 buffer taken from a solution prepared from 50 ml of 0.1

molar solution of monosodium phosphate and 29.1 ml of N/10 sodium hydroxide solution. 0.45 g (0.0072 mol) of sodium cyanoborohydride are added all at once. The reaction mixture is left at room temperature for 22 hours.

The excess sodium cyanoborohydride is decomposed by the addition of 6 ml of concentrated hydrochloric acid. The resulting solution is passed over an ion exchange resin (Dowex 50 H^+). After washing out the resin with distilled water until there are no chlorine ions present, the product fixed on the resin is removed by washing out with 1 litre of normal aqueous ammonia solution. The ammoniacal solution is concentrated to dryness under vacuum by water jet pump. The evaporation residue is the monoammonium salt of the desired product.
Weight obtained: 0.8 g (69.7%)

Analysis $C_{16}H_{23}N_3O_5$

	C%	H%	N%
Calculated	56.96	6.64	12.95
Found	57.79	6.69	12.70

The following Examples illustrate the invention.

EXAMPLE 1

1-{(S)-N-[(1RS)-1-carboxyethyl] -alanyl}-2-carboxyperhydroindole.

Step A

(2RS)-2-carboxyindoline.

31.5 g of the above indoline (86%) are obtained by saponification in 250 ml of normal sodium hydroxide solution and 150 ml of ethanol for 18 hours at room temperature of 43 g (0.224 mol) of the corresponding ethyl ester prepared according to E.J. COREY et al. (J. Amer. Chem. Soc. 1970 92, p. 2476).

The aqueous alcoholic solution is concentrated to ½, neutralised with 25 ml of 10N hydrochloric acid, and the precipitate formed is filtered, washed with water, and dried.

The crude acid is purified by being passed through an ion exchange resin column (Dowex 50 W x 8 H^+) and washed out with 2N aqueous ammonia solution. The ammonium salt obtained is dissolved in the minimum quantity of water and the acid precipitated by the theoretical amount of HCl. It is centrifuged, washed with water, and air-dried.

Analysis (of ammonium salt) $C_9H_{12}N_2O_2$

	C%	H%	N%
Calculated	59.99	6.71	15.54
Found	60.22	6.71	15.06
	59.93	6.71	15.29

Step B

(2S)-2-carboxyindoline.

60.5 g (0.37 mol) of (DL)-2-carboxyindoline prepared in Step A are added to a solution of 44.9 g (0.37 mol) of (+)-α-methylbenzylamine in 400 ml of anhydrous ethanol. The precipitate obtained is centrifuged and digested in 350 ml of anhydrous isopropanol under reflux. After cooling, the suspension is filtered, and the precipitate is washed with a little isopropanol and dried.

Weight of (L)-2-carboxyindoline, (+)-α-methylbenzylamine salt obtained 29.8 g.

$\alpha_D^{21} = 5.3^o$ (C = 1% ethanol).

The (2S)-2-carboxyindoline is prepared in a theoretical yield by dissolving 10 g of the above-mentioned salt

(0.029 mol) in 50 ml of water and acidifying it with 29 ml of normal hydrochloric acid.

The precipitate is centrifuged, washed with water, distilled, and dried. Optical purity : 96% (VPC after converting into the form of (-)-camphanic acid amide.

The (2R)-2-carboxyindoline was obtained by the same process, starting from (RS)-carboxyindoline and (-)-α-methylbenzylamine.

The absolute configurations of the (S) and (R) acids were determined as follows:

Analytical amounts (approx. 0.5 g) of each of the acids are converted into ethyl esters by treatment with thionyl chloride and ethanol according to the process described in Step C.

The esters are reduced by lithium aluminium hydride according to E.J. COREY (loc.cit.) to the corresponding primary alcohols, which are identified by their rotatory power with the alcohols described by E.J. COREY, the respective absolute configurations of which are known.

Step C

(2S)-2-ethoxycarbonylperhydroindole.

11 g of (L)-2-carboxyindoline, (+)-α-methylbenzylamine salt (0.032 mol) prepared in Step B are dissolved in 100 ml of water and converted into the corresponding acid by the addition of 32 ml of N HCl. The acid is centrifuged, washed with water and dried in a desiccator over phosphoric anhydride, then suspended in 50 ml of anhydrous ethanol. At a temperature of 0, +5°, 3.9 ml of thionyl chloride are added within 10 minutes whilst stirring, and stirring is continued for 1 hour at 25°C, then 1 hour at 50°C.

The mixture is left overnight at 25°, then concentrated to dryness under vacuum by water jet pump at 40° and taken up with 50 ml of anhydrous benzene and centrifuged.

The (2S)-2-ethoxycarbonylindoline hydrochloride obtained is hydrogenated in solution in 150 ml of water in the presence of 2 g of palladinised charcoal for 8 hours at 45°C under 50 kg/cm^2 pressure.

After cooling and filtration of the catalyst, the filtrate is evaporated to dryness. The residue is the

After 65 hours' stirring at 25°, the dicyclohexylurea formed is filtered and washed with ethyl acetate. The combined filtrates are washed successively with 80 ml of a saturated aqueous solution of NaCl, 2 x 40 ml of concentrated citric acid solution, 2 x 40 ml of a saturated aqueous solution of $NaHCO_3$, then again with 2 x 40 ml of NaCl solution.

The organic solution is dried over $CaSO_4$, filtered, concentrated to dryness under vacuum by water jet pump, and the residue is taken up in 100 ml of ethyl acetate. The solution is filtered to eliminate the last traces of dicyclohexylurea, and the filtrate which is concentrated to dryness leaves a residue which is the desired product in the form of a very viscous oil.

Weight : 3.8 g (81%)

Analysis $C_{19}H_{32}N_2O_5$

	C%	H%	N%
Calculated	61.93	8.75	7.60
Found	61.76	8.56	7.77

Step E

(2S)-N-[(S)-t-Boc-alanyl]-2-carboxyperhydroindole.

3.6 g (0.0098 mol) of ester obtained in Step D are dissolved in 30 ml of methanol in the presence of 11 ml of

normal aquaeous sodium hydroxide solution.

After 20 hours at 25°, the methanol is evaporated under vacuum by water jet pump and 60 ml of water are added. The solution is washed with 2 x 50 ml of ethyl acetate to eliminate the unsaponified material, then acidified with 11 ml of N hydrochloric acid. The while precipitate formed is extracted with 2 x 50 ml of ethyl acetate, which are combined and washed with water, dried over $CaSO_4$, filtered and concentrated to dryness. The residue is the desired product:

Weight : 1.9 g (57%)

Analysis $C_{17}H_{28}N_2O_5$

	C%	H%	N%
Calculated	59.98	8.29	8.23
Found	59.10	8.16	7.81

Step F

(2S)-1-[(S)-alanyl]-2-carboxyperhydroindole.

1.6 g (0.0047 mol) of acid prepared in the previous step (e) are stirred at a temperature of 0, + 5°C in solution in 10 ml of trifluoroacetic acid for 1 hour, and then for another 15 minutes at room temperature.

After being evaporated to dryness under vacuum by vane

pump, the residue dissolved in 15 ml of water is passed over an ion exchange resin column (Dowex W + $8H^+$). The column is washed out with 1 litre of 2 N aqueous ammonia solution. The washings are concentrated to dryness under vacuum. The residue obtained is the desired product.

Weight : 0.90 g (95%)

Analysis $C_{12}H_{20}N_2O_3$

	C%	H%	N%
Calculated	59.98	8.39	11.10
Found	58.53	8.24	11.43

Step G

(2S)-1-{(S)-N-[(1RS)-1-carboxyethyl]-alanyl}-2-carboxyperhydroindole.

0.7 g (0.00291 mol) of (2S)-N-[(S)-alanyl]-2-carboxyperhydroindole prepared in the previous step (F) and 1.67 g (0.0183 mol) of pyruvic acid are dissolved in 18 ml of normal aqueous sodium hydroxide solution and 40 ml of pH 7 buffer, and the solution obtained is subjected to reduction with 0.400 g (0.0064 mol) of sodium cyanoborohydride as described in Example 1, Step F.

After treatment with concentrated hydrochloric acid and being passed over an ion exchange resin (Dowex 50 H^+), the final ammoniacal washings, when evaporated to dryness,

leave 0.76 g (79%) of residue which is the desired product in the form of monoammonium salt.

Analysis $C_{15}H_{27}N_3O_5$

	C%	H%	N%
Calculated	54.70	8.26	12.76
Found	54.10	7.78	12.77

EXAMPLE 2

(2S)-1-{N-[2-((1RS)-1-ethoxycarbonylethylthio)-(1RS)-1-ethoxycarbonylethyl]-(S)-alanyl}-2-carboxyperhydroindole.

1 g (4.17 m mols) of (2S)-1-[(S)-alanyl]-2-carboxy-perhydroindole, prepared as described in Example 1, Step F, and 4.72 g (19 m mols) of ethyl [(1RS)-1-ethoxycarbonylethylthio]-pyruvate are dissolved in 50 ml of anhydrous ethanol in the presence of 15 g of molecular sieve 4 Å. After 45 minutes' stirring at room temperature, 0.25 g of sodium cyanoborohydride in solution in 2.25 ml of anhydrous ethanol are added within 6 hours.

After the molecular sieve has been separated off by filtration, the filtrate is concentrated to dryness under reduced pressure and the residue is dissolved in 100 ml of sulphuric ether. The solution is extracted with 2 x 100 ml of distilled water, then dried over calcium sulphate, filtered and chromatographed over 200 g of silica (Merck F 254), washing out with a 180/20 methylene chloride/

methanol mixture. 0.5 g (25%) of the desired product are obtained in the form of the sodium salt.

Analysis $C_{22}H_{35}N_2Na\ O_7S$

	C%	H%	N%	S%
Calculated	53.43	7.13	5.66	6.48
Found	53.28	7.09	5.19	5.92

The intermediate ethyl [(1RS)-1-ethoxycarbonylethylthio]-pyruvate is prepared by condensing ethyl bromopyruvate with (RS)-ethyl thiolactate in the presence of pyridine according to the process described for related derivatives in the J. of Heter. Chem. (1973) 10/4 p. 679-681).

$b.p._{.15}$ = 165-170

Yield 67%

EXAMPLE 3

(2S)-1-[N-(2-ethoxycarbonylmethylthio-(1RS)-1-ethoxycarbonylethyl)-(S)-alanyl]-2-carboxyperhydroindole.

Prepared as in Example 2, starting from 1 g (4.17 m mols) of (2S)-1-[(S)-alanyl]-2-carboxyperhydroindole, 4.45 g (1.9 mols) of ethyl ethoxycarbonylmethylthiopyruvate and 0.25 g of sodium cyanoborohydride.

After purification by chromatography, 0.26 g (14%) of the desired product are obtained.

Analysis $C_{21}H_{34}N_2O_7S$

	C%	H%	N%	S%
Calculated	55.00	7.47	6.11	6.99
Found	54.71	7.32	5.94	7.01

The intermediate ethyl ethoxycarbonylmethylthiopyruvate is prepared by condensing ethyl bromopyruvate with ethyl thioglycolate according to the process described by the reference quoted in Example 2.

$b.p._{15}$ = 165 -175 Yield 50%

The compounds prepared in the preceding Examples, and also other compounds of formula (I) prepared in a similar manner, have been collated in the Table which follows. For the sake of convenience, the symbols A and n are only mentioned for the values where A = a benzene ring and n = 1. For all the other compounds A means a saturated ring and n = 0 (perhydroindole of formula I').

The Table gives the characteristic values of the compounds with regard to infra-red (IR) and nuclear magnetic resonance (NMR) :

s is for singlet,

d is for doublet,

q is for quadruplet,

m is for multiplet.

TABLE

Compound No.	R_1	R_2	R_3	FORM (salt)
1 (Ex. 1)	CH_3	H	CH_3	ammonium salt
2	CH_3	C_2H_5	$-CH_2-S-CH(\text{cyclopropyl})_2$	———
3	CH_3	C_2H_5	$-CH_2-CH_2-CH(\text{cyclopropyl})_2$	acid maleate
4	CH_3	C_2H_5	CH_3	acid maleate
5	CH_3	C_2H_5	$-CH_2-S-CH(\text{cyclohexyl})_2$	sodium salt
6	CH_3	C_2H_5	$-CH_2-S-\underset{CH_3}{\overset{(RS)}{CH}}-COOC_2H_5$	sodium salt
7	CH_3	C_2H_5	$-CH_2-S-\underset{CH_3}{\overset{(S)}{CH}}-COOC_2H_5$	acid maleate
8	CH_3	C_2H_5	$-CH_2-CH(CH_3)_2$	sodium salt

TABLE (cont'd 1)

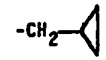
Compound No.	R_1	R_2	R_3	FORM (salt)
9 14 (Ex.3)	CH_3	C_2H_5	$-CH_2-S-CH_2-COOC_2H_5$	———
10	CH_3	C_2H_5	$n-C_4H_9$	sodium salt
11	CH_3	C_2H_5	$n-C_3H_7$	———
12	CH_3	C_2H_5		sodium salt
13	CH_3	C_2H_5	$i-C_3H_7$	sodium salt
14	CH_3	C_2H_5	C_2H_5	sodium salt
15	CH_3	C_2H_5	$n-C_5H_{11}$	sodium salt
16	CH_3	C_2H_5	$n-C_6H_{13}$	———
17	CH_3	C_2H_5	$n-C_8H_{17}$	trifluoroacetate.

TABLE (cont'd 2)

Comp.	I.R. (ν_s in cm^{-1})	NMR in $CDCl_3$: chemical shifts (ppm)/TMS
1	NH : 3500-2500 C=O : 1600	m. : 3H(4.8-4) Peaks : 18H(2.5-1.3) Peaks :
2		2H(6.35)
		Peaks : 17H(1.6-0.8) 10H(0.7-0.1) 6H(4.5-3.5) 3H(3.2-1.9) 2H(5.7-5.2)
3		Peaks : 21H(2.7-1) 11H(0.8-0.1) 6H(4.6-3.7) 4H(11.2)
4		s. : 2H(6.4)
		Peaks : 20H(2.7-1.1) 6H(4.7-3.9) 4H(10.3)
5	NH3700-3200 CO ester 1730 CO amide 1650-1600	s. : 2H(6.4) Peaks : 8H(4.7-3.2) 39H(2.5-1) d. : 2H (2.9)
6	NH3300 CO ester 1725 CO amide 1620	Peaks : 11H(4.5-2.6) 23H(2.5-1) s. : 2H(6.5) 4H exchangeable (11.1)
7		Peaks : 9H(4.7-3.2) 25H(2.5-1)
8	NH3600-2300 CO ester 1725 CO amide 1630	Peaks : 6H(3-4.5) 20H(1.2-2.5) d. : 6H(1)

TABLE (cont'd 3)

Comp.	I.R. (ν_s in cm^{-1})	NMR in $CDCl_3$: chemical shifts (ppm)/TMS
9	NH3700-2500 C=O ester 1720 C=O amide 1625	Peaks : 18H(2-1) 2H(2.5-2) q. : 4H(4.25) s. : 2H (3.4) 4H(4.5-3.2) d. : 2H(3) 2H exchangeable
10	NH3600-3100 C=O ester 1725 C=O amide 1620	Peaks : 6H(3-4.5) 27H(0.1-2.5)
11	NH 3300 C=O ester 1725 C=O amide 1620	Peaks : 24H(2.4-0.7) 6H(4.6-3.4) s. 2H(6.8)
12	NH 3300 C=O ester 1725 C=O amide 1610	Peaks : 25H(2.5-0) 6H(4.5-3)
13	NH 3300 C=O ester 1725 C=O amide	Peaks : 5H(4.5-3) 25H(0.7-2.5) 1H(2.9)
14	NH 3600-2500 C=O ester 1730 C=O amide 1610	Peaks : 6H(3-4.6) 23H(0.6-2.5)
15	NH 3300 C=O ester 1725 C=O amide 1610	Peaks : 7H(3-5) 28H(0.5-2.6)
16	NH_2^+ 3600-2400 C=O ester 1730 C=O amide 1650-1550	Peaks : 6H(3-4.7) 2H exchangeable (5.9) 30H(0.8-2.6)
17	NH_2^+ 3500-2300 C=O ester 1740 C=O amide 1650	Peaks : 6H(3.5-4.6) 3H exchangeable (8-9) 34H(0.6-2.7)

Pharmacological study of the compounds of the invention.

The compounds according to the invention were tested by i.v. or p.o. administration to dogs during consciousness.

The blood pressure of the dogs was measured by means of a pressure detector (Statham P 23 Db) after catheterisation of the aorta through the femoral artery. The findings were recorded by means of a recording apparatus (Brush 400).

Angiotensin I and angiotensin II were injected into the animals intravenously at a dosage of 0.3 γ/kg. The compounds according to the invention were then administered orally or intravenously at a dosage of from 1 to 5 mg/kg.

It was observed that there was inhibition of the hypertensive effect of angiotensin I ranging from 50 to 100% which occurred 30 to 90 minutes after administration and which remained at from 40 to 80% more than 6 hours after administration. Certain compounds remained active after 24 hours, which is not the case with any compound known hitherto (particularly captopril, which is the only commercially available compound). In addition, the compounds of the invention seem to have no toxic effect ($LD_0 >$ 500 mg/kg i.p. in mice).

EXAMPLE OF FORMULATION

(2S)-1-{N-[2-((1S)-1-ethoxycarbonylethylthio)-(1RS)-1-ethoxycarbonylethyl]-(S)-alanyl}-2-carboxyperhydroindole (maleate).....10 mg

wheat starch.....120 mg

cornstarch .....115 mg

casein treated with formaldehyde..... 20 mg

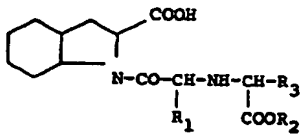
magnesium stearate..... 15 mg

talc..... 20 mg

for 1 tablet

CLAIMS

1. Compounds corresponding to the general formula:



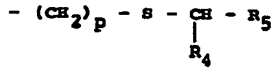
(I)

in which

R_1 represents a lower alkyl group having from 1 to 4 carbon atoms,

R_2 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms,

R_3 represents a linear or branched alkyl group, or a mono- or di-cycloalkyl-alkyl group, each of these groups having a maximum of 9 carbon atoms in total, or a substituted alkyl group of the formula:



in which

R_4 = H, (C_1-C_4)-lower alkyl or (C_3-C_6)-cycloalkyl,

R_5 = H, (C_1-C_4)-lower alkyl, (C_3-C_6)-cycloalkyl or alkoxycarbonyl, and

p = 1 or 2, in their racemic form or in the form of their optical isomers, and their salts obtained with a therapeutically compatible mineral or organic base, or their addition salts obtained with a pharmaceutically compatible mineral or organic acid.

2. Compounds according to claim 1, corresponding to formula (1), in which R_3 is a linear or branched (C_3-C_8)-alkyl group, a (C_4-C_8)-cycloalkylalkyl or a substituted alkyl of the formula:

$$-CH_2-S-\underset{\displaystyle R_4}{\overset{\displaystyle |}{CH}}-R_5$$

in which R_4 = H or (C_1-C_4)-alkyl and R_5 = $((C_1-C_4)$-alkoxy)-carbonyl.

3. Compounds according to claim 2, corresponding to the formula (1) in which R_1 is a methyl radical.

4. 1-{N-[2-(1-(RS)-ethoxycarbonylethylthio)-1-(RS)-ethoxycarbonylethyl]-(S)-alanyl}-2-(S)-carboxy-perhydroindole, its (S)-isomers and their maleate.

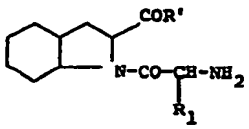
5. 1-(N-[1-(R,S)-ethoxycarbonyl-3-methylbutyl]-(S)-alanyl)-2-(S)-carboxy-perhydroindole, its (S)-isomer and their sodium salt.

6. 1-(N-[1-(R,S)-ethoxycarbonylpentyl]-(S)-alanyl)-2-(S)-carboxy-perhydroindole, its (S)-isomer and their sodium salt.

7. 1-(N-[1-(R,S)-ethoxycarbonylbutyl]-(S)-alanyl)-2-(S)-carboxy-perhydroindole, its (S)-isomer and their sodium salt.

8. 1-(N-[1-(R,S)-ethoxycarbonyl-2-cyclopropylethyl]-(S)-alanyl)-2-(S)-carboxy-perhydroindole, its (S)-isomer and their sodium salt.

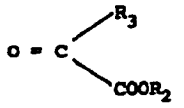
9. Process for the preparation of the compounds according to claim 1, characterised in that a dicarboxylic acid alkyl ester of the general formula II:



(II)

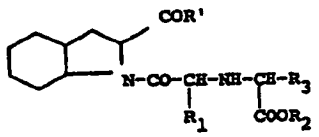
in which R_1 has the same meaning as in formula 1, and R' represents a hydroxy radical or a lower alkoxy radical, is subjected to a reductive alkylation reaction

with a compound of the general formula III:



(III)

in which the definition of the substituents R_2 and R_3 is the same as in claim 1, to obtain an amine of the general formula IV:



(IV)

in which R' has the meaning given above for formula II and the symbols R_1, R_2 and R_3 retain the meanings given previously, and, after reductive alkylation, this intermediate compound obtained is optionally subjected to customary deprotection processes, such as, for example, total or partial hydrolysis and/or hydrogenolysis, and is thus converted into a compound of the formula (I).

10. Pharmaceutical composition containing as active ingredient at least one compound according to any one of claims 1 to 8, in conjunction with an excipient or a therapeutically compatible non-toxic inert carrier.

11. Compounds substantially as hereinbefore described with reference to the Examples.

12. A process substantially as hereinbefore described with reference to the Examples.

13. A pharmaceutical composition substantially as hereinbefore described with reference to the Examples.

Dated this 29th day of September 1981

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